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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,344	04/05/2001	C. Frank Bennett	RTS-0147	1718

7590 04/03/2003

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	PAPER NUMBER
	9

DATE MAILED: 04/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Appl.

Office Action Summary	Application No.	Applicant(s)	
	09/828,344	BENNETT ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

Applicant's response filed February 3, 2003 has been considered. Applicants' cancellation of claims 11 and 16-20, and amendment of claims 1 and 15 has been considered and fully entered. Rejections and/or objections not reiterated from the previous office action mailed October 4, 2003, are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Response to Arguments

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weidmer et al. in view of Baracchini et al. These references are of record from the first Office action on the merits mailed October 3, 2002. However, Applicants' amendments necessitate a new grounds of rejection. Applicant's arguments with respect to the above listed claims have been considered, but some are considered moot in view of the new ground(s) of rejection; those arguments considered relevant to the instant rejection are addressed below.

The invention of the above listed claims is drawn to antisense oligonucleotide compounds that are targeted to and inhibit the expression of PLSCR1, and to sugar, base, or nucleobase

modifications thereof, including chimeras, and to pharmaceutical preparations containing said oligonucleotides.

Weidmer et al. teach the cDNA sequence of PLSCR1. Weidmer et al. teach that said cDNA sequence can used to create antisense sequences for the inhibition of PLSCR1 (for example, col. 2, lines 57-58, or col. 8 lines 29-34). Weidmer et al. does not teach antisense sequences that comprise phosphorothioate, sugar, or nucleobase modifications, or chimeras of these, or pharmaceutical preparations comprising said compounds.

Baracchini et al. teach antisense oligonucleotide compounds comprising sugar (2'-O methoxyethyl; see abstract), internucleoside (phosphorothioate; col. 6, line 38) and nucleobase (5-methylcytosine; col. 7 line 23) modifications, and chimeras (col. 8, line 10), and pharmaceutical preparations comprising said compounds (col. 4). Baracchini et al. also teach that preferable targeting sites of mRNA transcripts specifically include the 5'-untranslated region, the start codon region, the coding region, the stop codon region, and the 3'-untranslated region (cols. 9 and 10).

It would have been obvious to one of ordinary skill in the art to make antisense oligos to inhibit PLSCR1, because Weidmer et al. expressly teach that antisense oligos can be made from the human PLSCR1 cDNA to inhibit expression of the instant PLSCR1 target sequence of SEQ ID NO: 3. It also would have been obvious to one of ordinary skill in the art to target the 5'-untranslated region, a coding region, or a 3'-untranslated region as taught by Baracchini et al., and to incorporate modifications as taught by Baracchini et al. into antisense compounds.

One would have been motivated to make such antisense compounds because Weidmer et al. expressly teach that antisense compounds can be made and used in the inhibition of applicants' instant PLSCR1 target gene of SEQ ID NO: 3. One of ordinary skill in the art would also have been motivated to target the 5'-untranslated region, the coding region, and the 3'-untranslated region of applicants' instant PLSCR1 target gene of SEQ ID NO: 3, because Baracchini et al. teach that these are preferred sites for targeting gene transcripts using antisense-mediated inhibition. Baracchini et al. also teach motivation to introduce the above listed modifications to said antisense compounds, because such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation.

One would have had a reasonable expectation of success given that antisense-mediated inhibition of PLSCR1 was previously taught by Weidmer et al. and since Baracchini et al. teach and exemplify such antisense mediated inhibition, and since the steps involved are routine to one of ordinary skill in the art. Furthermore, one of ordinary skill would have had a reasonable expectation of success in modifying such compounds to enhance the activity of antisense compounds as taught by Baracchini et al., because such steps are explicitly taught and routinely performed by one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

In regards to applicants' arguments, applicants' state that, when viewed alone, none of Weidmer et al. or Baracchini et al. teach or suggest antisense compounds targeted to the specific regions of the PLSCR1 transcript of SEQ ID NO: 3 as presently claimed. This argument is not

agreed with. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is acknowledged that the references when viewed individually do not teach the presently claimed invention; however, the test for obviousness is what the combined teaching of the prior art would have suggested to those of ordinary skill in the art. As indicated above, one would have been motivated to make such compounds because Weidmer et al. expressly teach antisense inhibition of the human PLSCR1 gene that is identical to applicants' claimed PLSCR1 target of SEQ ID NO: 3. It thus follows that one of ordinary skill in the art would have been motivated to make antisense molecules targeted to the instant PLSCR1 target of SEQ ID NO: 3.

Applicants also argue that the reference of Weidmer et al. does not teach the use of any specific antisense compound to inhibit expression of the human PLSCR1, and that therefore there is no reasonable expectation of success. This argument is not considered convincing, because Baracchini et al. teach the steps required to make and use antisense oligos to inhibit transcripts of known sequence, and because Weidmer et al. teach both the cDNA of applicants' instant PLSCR1 target gene of SEQ ID NO: 3, and that antisense transcripts targeted to this PLSCR1 gene can be made by one of skill in the art (for example at col. 8, lines 29-34). Furthermore, such steps are routine to one of ordinary skill in the art. Applicants have asserted that there is no reasonable expectation of success, and have provided no rationale or evidence as to why this combination of references would refute the statement of Weidmer et al. and the

teachings of Baracchini et al. that support a reasonable expectation of success. Accordingly, in view of the references above, applicants arguments are not considered convincing. Thus, the invention of the above claims stands rejected under 35 U.S.C. § 103(a) for the reasons provided.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
April 1, 2003